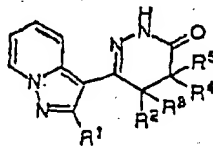


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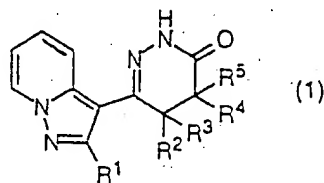


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(54) Title: PYRAZOLOPYRIDYLPYRIDAZINONE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF		
(54) 発明の名称 ビラゾロピリジンピリダジノン誘導体及びその製造法		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>(57) Abstract</p> <p>Novel pyrazolopyridylpyridazinone derivatives characterized by being represented by general formula (1) and pharmacologically acceptable salts thereof, which exhibit a phosphodiesterase inhibiting activity and have a selective potent bronchodilating effect on the respiratory tract; a process for the preparation of them; and bronchodilators containing the same as the active ingredient; wherein R¹ is C₁-C₄ lower alkyl or C₃-C₆ cycloalkyl; and R², R³, R⁴ and R⁵ are each independently hydrogen, C₁-C₄ lower alkyl or phenyl, or alternatively R³ and R⁵ may be united to form a double bond.</p> </div> <div style="width: 45%; text-align: center;">  <p>(1)</p> </div> </div>		

選択的に作用し、強力なホスホジエステラーゼ阻害作用を介し気管支拡張作用を発現する薬剤の開発は、副作用の少ない理想的な薬剤として強く望まれている。

本発明者らは、ホスホジエステラーゼ阻害活性を有し、気道に選択的で強力な気管支拡張作用を有する化合物について鋭意研究を重ねた結果、これまでに知られている気管支拡張薬とは構造を異にした新規なピラゾロピリジンピリダジノン誘導体が、安全性も高く、気道に選択的で強力な気管支拡張作用を有することを見出し、本発明を完成した。

即ち、本発明は一般式(1)

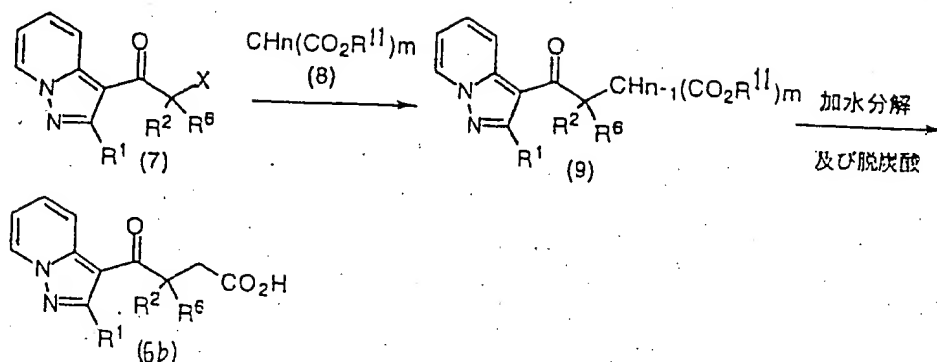


[式中、 R^1 は炭素数1～4の低級アルキル基、炭素数3～6のシクロアルキル基を、 R^2 、 R^3 、 R^4 、 R^5 は同一又は異なって、水素原子、炭素数1～4の低級アルキル基、フェニル基を示すか、または、 R^3 と R^5 が結合して二重結合を形成しても良い] で表されることを特徴とするピラゾロピリジンピリダジノン誘導体及び薬理学的に許容しうる塩、並びにそれらの少なくとも一種以上を有効成分とする気管支拡張薬である。

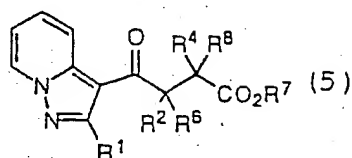
本発明における一般式(1)で表される化合物の薬理学的に許容される塩には、塩酸塩、臭化水素酸塩、クエン酸塩、メタンスルホン酸塩、酒石酸塩のような酸付加塩が挙げられる。

また、本発明の一般式(1)において、「低級アルキル基」とは、

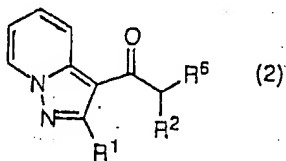
合成経路 3



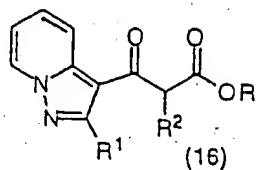
合成経路 1 で一般式 (5)



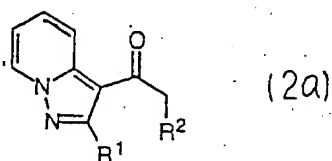
[式中、 R^1 、 R^2 、 R^4 、 R^6 、 R^8 は前述の通り、 R^7 は炭素数 1～3 の低級アルキル基を示す] で表される化合物は、一般式 (2) で表される化合物を一般式 (4) で表される化合物と反応させることによって製造することができる。



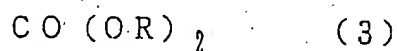
合成経路 2 で一般式 (16)



[式中、 R^1 、 R^2 は前述の通り、 R は炭素数 1～3 の低級アルキル基を示す] で表される化合物は、下記一般式 (2a) で表される化合物を一般式 (3) で表される化合物と反応させることによって製造することができる。



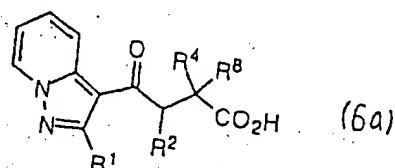
[式中、 R^1 、 R^2 は前述の通り]



[式中、 R は前述の通り]

反応は、カリウムターボトキシド、水素化カリウム等の無機塩基、好ましくは水素化ナトリウムの存在下、一般式 (3) の化合物を溶媒量用い、反応温度としては加熱還流下に行うのが好ましい。

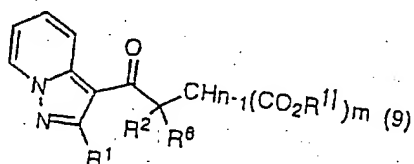
特に限定されないが、0℃～溶媒還流温度で行うことが好ましい。
合成経路2で一般式(6a)



[式中、 R^1 、 R^2 、 R^4 、 R^8 は前述の通り] で表される化合物は、上記一般式(17)で表される化合物を加水分解及び脱炭酸することによって製造することができる。

加水分解及び脱炭酸は、酸触媒の場合、塩酸または臭化水素酸を用いて80～120℃に加熱して行うのが好ましい。また、アルカリ触媒の場合、水酸化ナトリウム水溶液または水酸化カリウム水溶液を用い、メタノール、エタノール等のアルコール系溶媒や、テトラヒドロフラン、ジメチルホルムアミド等の溶媒中、室温下で行うのが好ましい。

合成経路3で一般式(9)



[式中、 R^1 、 R^2 、 R^6 は前述の通り、 R^{11} は炭素数1～3の低級アルキル基を、 (n, m) は(1, 3)及び(2, 2)の整数の組合せを示す] で表される化合物は、一般式(7)で表される化合

記一般式(9)で表される化合物を加水分解及び脱炭酸することによって製造することができる。

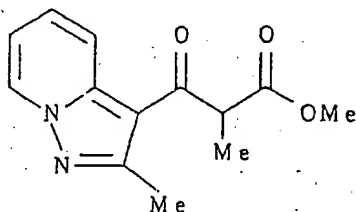
加水分解及び脱炭酸は、酸触媒の場合、塩酸または臭化水素酸を用いて80～120℃に加熱して行うのが好ましい。また、アルカリ触媒の場合、水酸化ナトリウム水溶液または水酸化カリウム水溶液を用い、メタノール、エタノール等のアルコール系溶媒や、テトラヒドロフラン、ジメチルホルムアミド等の溶媒中、室温下で行うのが好ましい。

発明を実施するための最良の形態

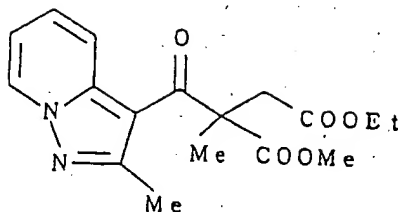
次に本発明を具体例によって説明するが、これらの例によって本発明が限定されるものではない。また、本発明化合物は、ジヒドロピリダジノン環の4位、5位に不斉炭素を持つ場合に光学異性体が存在するが、これらもすべて包含するものである。

実施例1

2-メチル-3-(2-メチルピラゾロ[1,5-a]ピリジン-3-イル)-3-オキソプロピオン酸メチルエステル



2-メチル-3-プロピオニルピラゾロ[1,5-a]ピリジン(5.28g)を炭酸ジメチル(100ml)に溶解し、水素化ナトリウム(3.37g)を加え、8時間加熱還流した。水浴にて冷却下、酢酸を加え、ついで水で希釈後塩化メチレンで抽出した。有機層を無水硫

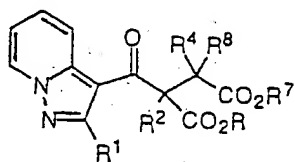


実施例 1 の化合物 (5.13 g) を DMF (70 ml) に溶解し、水素化ナトリウム (1.00 g) を加え室温にて 1 時間攪拌した。氷浴にて冷却し、2-ブロモ酢酸エチル (2.77 ml) を加え 18 時間室温に昇温するまで攪拌後、飽和塩化アンモニウム水溶液を加え、水で希釈後エーテルで抽出した。有機層を水、飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥した後、溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー (展開溶媒 酢酸エチル: n-ヘキサン = 1:2) にて精製した。目的物 (4.63 g) を黄色油状物として得た。

実施例 10-16

実施例 2~8 の化合物を原料として、2-ブロモ酢酸エチル、または 2-ブロモ酢酸メチル、または 2-ブロモプロピオン酸メチルを用い、実施例 9 と同様に行い下記化合物を得た (表 2)。

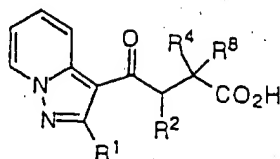
[表 2]



実施例18-24

実施例17と同様に行い下記化合物を得た(表3)。

[表3]



実施例	R ¹	R ²	R ⁴	R ⁸	Yield (%)	性 状
18	Me	Et	H	H	80	褐色アモルファス
19	Et	Me	H	H	90	褐色アモルファス
20	Pr	Me	H	H	58	淡黄色アモルファス
21	i-Pr	H	Me	H	99	淡桃色粉末
22	i-Pr	Me	H	H	53	無色粉末
23	i-Pr	Et	H	H	65	淡黄色アモルファス
24	cyclo-Pr	Me	H	H	60	褐色アモルファス

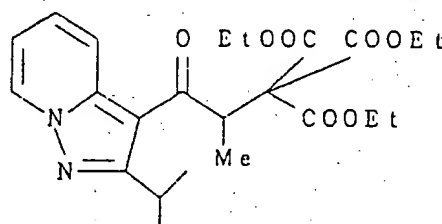
実施例25

4-(2-イソプロピルピラゾロ[1,5-a]ピリジン-3-イル)-3-フェニル-4-オキソ酪酸メチルエステル

メチレンで抽出した。有機層を無水硫酸ナトリウムで乾燥した後、溶媒を減圧留去し、目的物 (1.50 g) を無色粉末として得た。

実施例27

2, 2-ジエトキシカルボニル-4-(2-イソプロピルピラゾロ [1, 5-a] ピリジン-3-イル)-3-メチル-4-オキソ酪酸エチルエステル



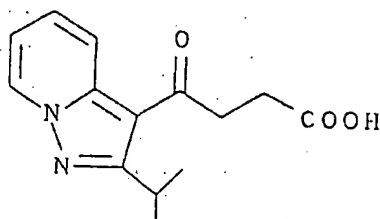
トリエトキシカルボニルメタン (1.53 g) を DMF (20 ml) に溶解し、水素化ナトリウム (0.28 g) を加え室温にて 0.5 時間撹拌した。3-(2-ブロモプロピオニル)-2-イソプロピルピラゾロ [1, 5-a] ピリジン (1.77 g) を加え、1 時間室温にて撹拌後、80~100℃にてさらに 7 時間加熱撹拌した。反応液に飽和塩化アンモニウム水溶液を加え、水で希釈後エーテルで抽出した。有機層を水、飽和食塩水で洗浄後、無水硫酸ナトリウムで乾燥した後、溶媒を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー (展開溶媒 酢酸エチル: n-ヘキサン=1:2) にて精製した。目的物 (0.67 g) を黄色油状物として得た。

実施例28

2-エトキシカルボニル-4-(2-イソプロピルピラゾロ [1, 5-a] ピリジン-3-イル)-4-オキソ酪酸エチルエステル

実施例30

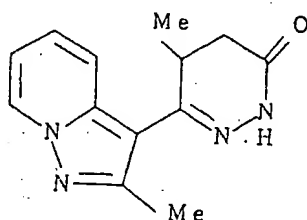
4 - (2 - イソプロピルピラゾロ [1, 5 - a] ピリジン - 3 -
イル) - 4 - オキソ酪酸



実施例28の化合物 (0.72 g) を用い実施例17と同様に行い、目的化合物 (0.52 g) を無色粉末として得た。

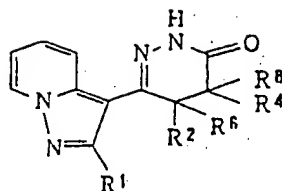
実施例31

6 - (2 - メチルピラゾロ [1, 5 - a] ピリジン - 3 - イル)
- 5 - メチル - 4, 5 - ジヒドロ - 3 (2 H) - ピリダジノン



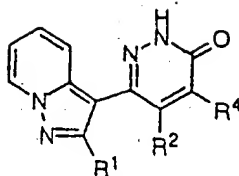
実施例17の化合物 (2.76 g) とヒドラジン 1 水和物 (0.90 g) をエタノール (30ml) に溶解し、3時間加熱還流した。反応液を減圧留去し、残渣をシリカゲルカラムクロマトグラフィー (展開溶媒 塩化メチレン:エタノール=10:1) にて精製した。目的物 (2.04 g) を無色粉末として得た。このものはイソプロピルエーテルから再結晶すると、無色プリズム晶が得られた。融点 146 ~ 147°C

[表 4]



実施例	R ¹	R ²	R ⁴	R ⁶	R ⁸	Yield(%)	融点(℃) (再結晶溶媒)	元素分析値 計算値/実測値 C, H, N
32	Me	Et	H	H	H	80	138~140 /-Pr ₂ O	C ₁₄ H ₁₆ N ₄ O 55.61 6.29 21.86 55.70 6.31 21.72
33	Et	Me	H	H	H	79	131~132 /-Pr ₂ O	C ₁₄ H ₁₆ N ₄ O 55.61 6.29 21.86 55.74 6.22 21.85
34	Pr	Me	H	H	H	66	141~142 /-Pr ₂ O	C ₁₅ H ₁₈ N ₄ O 55.65 6.71 20.73 55.43 6.64 20.50
35	i-Pr	H	H	H	H	86	213.5~215.5 EtOH	C ₁₄ H ₁₆ N ₄ O 55.61 6.29 21.86 55.33 6.31 21.70
36	i-Pr	Me	H	H	H	50	119~122 /-Pr ₂ O	C ₁₅ H ₁₈ N ₄ O 55.65 6.71 20.73 55.54 6.73 20.57
37	i-Pr	Et	H	H	H	77	147 /-Pr ₂ O	C ₁₆ H ₂₀ N ₄ O 57.58 7.09 19.70 57.47 7.05 19.62
38	i-Pr	Ph	H	H	H	55	192~193 /-Pr ₂ O	C ₂₀ H ₂₀ N ₄ O 71.49 6.12 16.67 71.81 6.25 16.27 但し 1/5 H ₂ O 付加物
39	i-Pr	H	Me	H	H	86	207~208 EtOH	C ₁₅ H ₁₈ N ₄ O 55.65 6.71 20.73 55.65 6.58 20.74
40	cyclo-Pr	Me	H	H	H	79	134 /-Pr ₂ O	C ₁₅ H ₁₈ N ₄ O 57.15 6.01 20.88 57.31 6.07 20.85

[表 5]



実施例	R ¹	R ²	R ⁴	Yield(%)	融点 (°C) (再結晶溶媒)	元素分析値 計算値/実測値
42	i-Pr	H	Me	71	216-217 AcOEt	C ₁₅ H ₁₆ N ₄ O 67.15 6.01 20.88 66.95 5.97 20.82
43	i-Pr	H	H	73	225 AcOEt	C ₁₄ H ₁₄ N ₄ O 65.66 5.59 21.88 65.43 5.56 21.64 但し 1/10 H ₂ O 付加物

実施例44

(-) - 6 - (2-イソプロピルピラゾロ [1, 5-a] ピリジン-3-イル) - 5-メチル-4, 5-ジヒドロ-3 (2H) -ピリダジノン及び (+) - 6 - (2-イソプロピルピラゾロ [1, 5-a] ピリジン-3-イル) - 5-メチル-4, 5-ジヒドロ-3 (2H) -ピリダジノン

実施例36の化合物 (1.31g) を65mlのエタノールとヘキサンの混液 (1:4) に溶解し、この溶液をHPLCにて自動分取した (光学分割カラム: Chiralcell ODダイセル化学工業製、移動層ヘキサン: イソプロパノール = 9:1、注入量1ml、流速24ml/min、検出波長 293nm)。得られた各フラクションの化合物をジイソプロピルエーテルで再結晶し、前部流出フラクションより (-) 体 530mg、後部流出フラクションより (+) 体 560mgをいずれも無色粉末とし

ーゼを不活化、反応を停止した。被験化合物は基質と同時に試験管に添加した。

2) E I Aによる定量

酵素液による分解を受けずに残存した c A M P または c G M P を、c A M P 定量用または c G M P 定量用の E I A キット（アマシャム社製、England）を用いて定量し、酵素反応を 50% 抑制するのに必要な被験物質量を $I C_{50}$ として求めた結果を表 6 に示す。

[表 6]

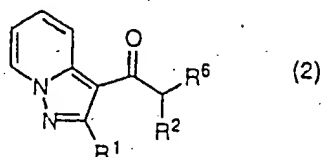
	$I C_{50}(\mu g/ml)$						
	気道				心臓		
	II	III	IV	V	I	II	III
実施例 36	>30	4	5	0.1	>30	>30	5

産業上の利用可能性

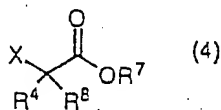
本発明化合物は気道由来のホスホジエステラーゼ、特にホスホジエステラーゼ V に対して選択的に抑制効果を示す。

理学的に許容しうる塩の少なくとも一種類以上を有効成分とする気管支拡張薬。

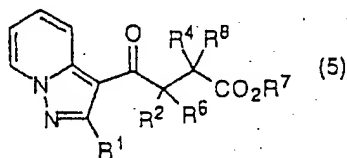
3. 一般式(2)

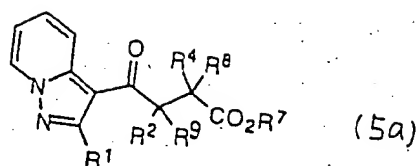


[式中、 R^1 は炭素数1～4の低級アルキル基、炭素数3～6のシクロアルキル基を、 R^2 、 R^6 は同一又は異なって、水素原子、炭素数1～4の低級アルキル基、フェニル基を示す] で表される化合物に一般式(4)



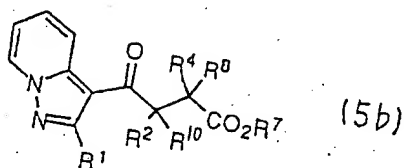
[式中、 R^4 、 R^8 は同一又は異なって、水素原子、炭素数1～4の低級アルキル基、フェニル基を、 R^7 は炭素数1～3の低級アルキル基を、Xはハロゲン原子を示す] で表される化合物を反応させることを特徴とする一般式(5)



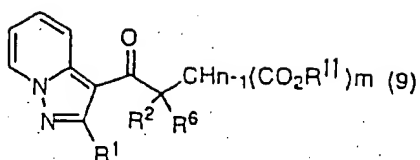


[式中、 R^1 、 R^2 、 R^4 、 R^7 、 R^8 は前述の通り、 R^9 は炭素数 1～3 の低級アルコキシカルボニル基を示す] で表される化合物の製造方法。

5. 一般式 (5.b)

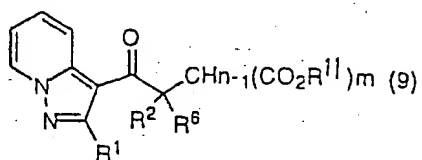


[式中、 R^1 は炭素数 1～4 の低級アルキル基、炭素数 3～6 のシクロアルキル基を、 R^2 、 R^4 、 R^8 は同一又は異なって、水素原子、炭素数 1～4 の低級アルキル基、フェニル基を、 R^7 は炭素数 1～3 の低級アルキル基を、 R^{10} は水素原子、炭素数 1～4 の低級アルキル基、フェニル基、炭素数 1～3 の低級アルコキシカルボニル基を示す] で表される化合物を加水分解し、必要ならば脱炭酸することを特徴とする一般式 (6)

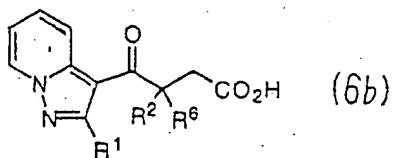


[式中、 R^1 、 R^2 、 R^6 、 R^{11} 、 n 、 m は前述の通り]で表される化合物の製造方法。

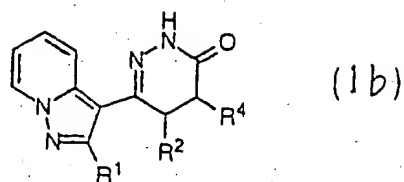
7. 一般式(9)



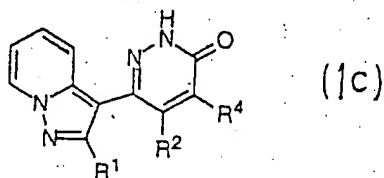
[式中、 R^1 は炭素数1～4の低級アルキル基、炭素数3～6のシクロアルキル基を、 R^2 、 R^6 は同一又は異なって、水素原子、炭素数1～4の低級アルキル基、フェニル基を、 R^{11} は炭素数1～3の低級アルキル基を、 (n, m) は(1, 3)及び(2, 2)の整数の組合せを示す]で表される化合物を加水分解及び脱炭酸することを特徴とする一般式(6b)



9. 一般式 (1b)



〔式中、R¹ は炭素数 1～4 の低級アルキル基、炭素数 3～6 のシクロアルキル基を、R²、R⁴ は同一又は異なって、水素原子、炭素数 1～4 の低級アルキル基、フェニル基を示す〕で表される化合物を酸化することを特徴とする一般式 (1c)



〔式中、R¹、R²、R⁴ は前述の通り〕で表される化合物の製造方法。

Specification

Pyrazolopyridylpyridazinone Derivatives and the Production Method Thereof

Technical Field

The present invention pertains to new pyrazolopyridylpyridazinone derivatives and the production method thereof, which exhibit a phosphodiesterase inhibitory effect and a potent bronchodilating effect which is selective to the airway.

Technical Background

Patent Application Publication Nos. Koukai Hei 2-243689 and Koukai Hei 4-253978 disclose compounds in which their pyrazolopyridine ring has a substituent of a dihydropyridazinone and pyridazinone group at position 3. However, the compounds which are claimed in these Koukai Patent Publications are limited to those with an aryl group such as a benzene derivative, as the second position substituent. They do not include the compounds of the present invention in which the substituent is an alkyl group. Moreover, Patent Application Publication No. Koukai Hei 8-12673 discloses pyrazolopyridine derivatives having a bronchodilating effect. However, the compounds disclosed therein have completely different structures from those of the compounds in the present invention.

Since it was found that an increase of cyclic AMP or GMP in cells causes a bronchodilating effect, attention has been given to phosphodiesterase inhibitors, which are enzymes to decompose cyclic AMP and GMP, as a bronchodilating medicine. Examples of a general pharmaceutical, which functions as a phosphodiesterase inhibitor, include theophylline. However, theophylline has a low selectivity towards a target organ. Hence, when theophylline is used for the purpose of causing a bronchodilating effect on patients such as asthma patients, undesired effects such as an increased heart beat, vomiting, effects on the nerve center and so forth, occur. Development of pharmaceuticals which selectively act on the target organ, the airway, and manifest a

bronchodilating effect through their potent phosphodiesterase inhibitory effect are strongly desired. Such pharmaceuticals would have fewer side effects and be ideal.

Results of focused and dedicated research by the inventors for compounds having a phosphodiesterase inhibitory effect and a potent bronchodilating effect which is selective to the airway found the following. It was found that new pyrazolopyridylpyridazinone derivatives with different structures from those of previously known bronchodilating medicines are highly safe and have a potent and bronchodilating effect selective to the airway. Thus, the present invention was completed.

In other words, the present invention relates to pyrazolopyridylpyridazinone derivatives having a characteristic in that they are expressed by general formula (1),

Formula (1) (1)

pharmacologically acceptable salts thereof, and bronchodilators containing at least one of such materials as the active ingredient, [wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^3 , R^4 , and R^5 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 3 carbon atoms, or a phenyl group; and moreover, R^3 and R^5 may bond to each other to form a double bond.]

Examples of pharmacologically acceptable salts of the compounds expressed by general formula (1) in the present invention include salts with an acid such as hydrochloride, hydrobromate, citrate, methanesulfonate, and tartarate.

In general formula (1) of the present invention, "a lower alkyl group" represents a straight or branched hydrocarbon having 1 ~ 4 carbon atoms such as methyl, ethyl, or propyl; "a cycloalkyl group" represents a cyclic hydrocarbon having 3 ~ 6 carbon atoms. Moreover, examples of "a halogen atom" include chlorine, bromine, and iodine.

According to the present invention, the compounds in which R^3 and R^5 do not form a double bond among the compounds expressed by the above general formula (1), in other words, the compounds which are expressed by general formula (1a)

Formula (1a), (1a)

[wherein R^1 is the same as previously described; R^2 , R^4 , R^6 , and R^8 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group,] can be produced by reacting the compounds expressed by general formula (6) below with hydrazine,

Formula (6) (6)

[wherein R^1 , R^2 , R^4 , R^6 , and R^8 are the same as previously described.]

Such a reaction can take place as an example, in benzene, toluene, acetic acid, ethanol. The reaction temperature may be at room temperature or solvent reflux temperature, or therebetween. Here, it is preferred to use ethanol as a reactive solvent and the heat reflux temperature as a reaction temperature.

The compounds in which R^3 and R^5 are bonded to each other and form a double bond, in other words, the compounds which are expressed by general formula (1c)

Formula (1c), (1c)

[wherein R^1 , R^2 , and R^4 are the same as previously described,] can be produced by oxidizing the compounds expressed by general formula (1b) below,

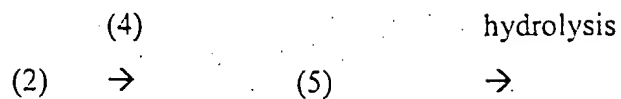
Formula (1b) (1b)

[wherein R^1 , R^2 , and R^4 are the same as previously described.]

It is preferred that the reaction takes place in an acetic acid solvent and bromine is used for the reaction. It is preferred that the reaction temperature is 50 ~ 60 degrees Celsius.

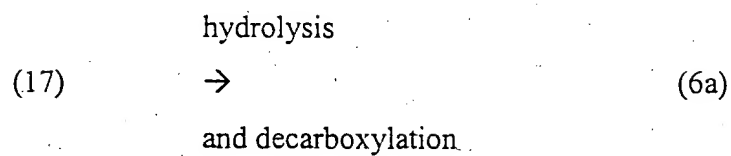
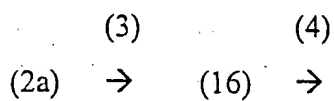
The compounds expressed by the above general formula (6) can be produced using the three processes below.

Synthesis process 1

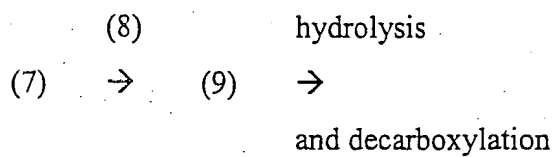


(6)

Synthesis process 2



Synthesis process 3



(6b)

In synthesis process 1, the compounds expressed by general formula (5),

Formula (5) (5)

[wherein R^1 , R^2 , R^4 , R^6 , and R^8 are the same as previously described; and R^7 is a lower alkyl group having 1 ~ 3 carbon atoms,] can be obtained by reacting the compounds expressed by general formula (2) with the compounds expressed by general formula (4),

Formula (2) (2)

[wherein R^1 , R^2 , and R^6 are the same as previously described,]

Formula (4) (4)

[and wherein X represents a halogen atom; and R^4 , R^7 , and R^8 are the same as previously described.]

The reaction takes place under the presence of an inorganic base such as potassium t-butoxide or potassium hydride, or more preferably sodium hydride, using tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or even more preferably dimethylformamide as a reaction solvent. The reaction temperature is not particularly restricted. However, it is preferred that the reaction take place at 0 degree Celsius ~ the solvent reflux temperature.

In synthesis process 1, the compounds expressed by general formula (6),

Formula (6) (6)

[wherein R^1 , R^2 , R^4 , R^6 , and R^8 are the same as previously described,] can be obtained by hydrolyzing the compounds expressed by general formula (5).

When the hydrolysis is performed with an acidic catalysis, it is preferred that it take place using hydrochloric acid or hydrobromic acid while the solution is heated to 80 ~ 120 degrees Celsius. Moreover, when the hydrolysis is performed with a basic catalysis, it is preferred that it take place using a sodium hydroxide aqua solution or a potassium hydroxide aqua solution with an alcohol solvent such as methanol or ethanol, or a solvent such as tetrahydrofuran or dimethylformamide at room temperature.

In synthesis process 2, the compounds expressed by general formula (16),

Formula (16) (16)

[wherein R^1 and R^2 are the same as previously described; and R is a lower alkyl group having 1 ~ 3 carbon atoms,] can be obtained by reacting the compounds expressed by general formula (2a) below, with the compounds expressed by general formula (3),

Formula (2a) (2a)

[wherein R^1 and R^2 are the same as previously described,]

$CO(OR)_2$ (3)

[and wherein R is the same as previously described.]

The reaction takes place under the presence of an inorganic base such as potassium t-butoxide or potassium hydride, or more preferably sodium hydride, using the compounds expressed by general formula (3) in the same amount as that of the solvent. As for the reaction temperature, it is preferred that this temperature is suitable for reflux by heating.

In synthesis process 2, the compounds expressed by general formula (17),

Formula (17) (17)

[wherein R, R^1 , R^2 , R^4 , R^7 , and R^8 are the same as previously described,] can be obtained by reacting the compounds expressed by general formula (16) with the compounds expressed by general formula (4),

Formula (16) (16)

[wherein R, R^1 and R^2 are the same as previously described,]

Formula (4)

(4)

[and wherein X, R⁴, R⁷, and R⁸ are the same as previously described.]

The reaction takes place under the presence of an inorganic base such as potassium t-butoxide or potassium hydride, or more preferably sodium hydride, using tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or even more preferably dimethylformamide as a reaction solvent. The reaction temperature is not particularly restricted. However, it is preferred that the reaction take place at 0 degree Celsius ~ the solvent reflux temperature.

In synthesis process 2, the compounds expressed by general formula (6a),

Formula (6a)

(6a)

[wherein R¹, R², R⁴, R⁶, and R⁸ are the same as previously described,] can be obtained by hydrolyzing and decarboxylating the compounds expressed by general formula (17).

When the hydrolysis and decarboxylation are performed with an acidic catalysis, it is preferred that they take place using hydrochloric acid or hydrobromic acid while the solution is heated to 80 ~ 120 degrees Celsius. Moreover, when the hydrolysis and decarboxylation are performed with a basic catalysis, it is preferred that they take place using a sodium hydroxide aqua solution or a potassium hydroxide aqua solution with a alcohol solvent such as methanol or ethanol, or a solvent such as tetrahydrofuran or dimethylformamide at room temperature.

In synthesis process 3, the compounds expressed by general formula (9),

Formula (9)

(9)

[wherein R¹, R² and R⁶ are the same as previously described; R¹¹ is a lower alkyl group having 1 ~ 3 carbon atoms; and (n, m) is a combination of integers, (1, 3) or (2, 2),] can be obtained by reacting the compounds expressed by general formula (7) with the compounds expressed by general formula (8),

Formula (7)

(7)

[wherein X, R¹, R² and R⁶ are the same as previously described,] with the compounds expressed by general formula (8),



[wherein the combination of (n, m) and R¹¹ are the same as previously described.]

The reaction takes place under the presence of an inorganic base such as potassium t-butoxide or potassium hydride, or more preferably sodium hydride, using tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, or even more preferably dimethylformamide as a reaction solvent. The reaction temperature is not particularly restricted. However, it is preferred that the reaction take place at 0 degree Celsius ~ the solvent reflux temperature.

In synthesis process 3, the compounds expressed by general formula (6b),

Formula (6b)

(6b)

[wherein R¹, R², and R⁶ are the same as previously described,] can be obtained by hydrolyzing and decarboxylating the compounds expressed by the above general formula (9).

When the hydrolysis and decarboxylation are performed with an acidic catalysis, it is preferred that they take place with hydrochloric acid or hydrobromic acid while the solution is heated to 80 ~ 120 degrees Celsius. Moreover, when the hydrolysis and decarboxylation are performed with a basic catalysis, it is preferred that they take place using a sodium hydroxide aqua solution or a potassium hydroxide aqua solution with an alcohol solvent such as methanol or ethanol, or a solvent such as tetrahydrofuran or dimethylformamide at room temperature.

The Best Form to Exemplify the Invention

Next, the present invention is explained with concrete examples. However, the present invention is not restricted by these examples. Moreover, when the compounds of the present invention have asymmetric carbon atoms at the fourth and fifth position of their dihydropyridazinone, optical isomers would exist. These optical isomers are included in the present invention.

Example 1

3-Methyl-3-(2-methylpyrazolo[1, 5-a]pyridine-3-yl)-3-oxopropionic Acid Methyl Ester

(Formula)

3-Methyl-3-propionylpyrazolo[1, 5-a]pyridine (5.28g) was dissolved in dimethyl carbonate (100ml). Then, sodium hydride (3.37g) was added and the mixture was refluxed by heating for eight hours. As it was chilled in an ice bath, acetic acid was added. Subsequently water was added to dilute the solution. Then, extraction was performed using methylene chloride. After the organic layer was dried using anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residuum was purified using silica gel column chromatography (developing solvent = ethyl acetate : n-hexane = 1:3 ~ 1:1). The target material (5.13g) was obtained in a yellow and oily form.

Example 2-8

In a similar manner as in Example 1, the compounds listed below (Table 1) were obtained.

Table 1

(formula)

Example	R ¹	R ²	R	Yield (%)	Properties
2	Me	Et	Me	91	Oily material with light yellow color
3	Et	Me	Me	93	Oily material with light yellow color
4	Pr	Me	Me	54	Oily material with yellow color
5	i - Pr	H	Me	94	Powder material with light yellow color
6	i - Pr	Me	Me	91	Oily material with brown color
7	i - Pr	Et	Me	87	Oily material with yellow color
8	cyclo-Pr	Me	Me	46	Oily material with brown color

Example 9

4-(2-Methylpyrazolo[1, 5-a]pyridine-3-yl)-3-methoxycarbonyl-3-methyl-4-oxobutyric Acid Ethyl Ester

(Formula)

The compound of Example 1 (5.13g) was dissolved in DMF (70ml). Then, sodium hydride (1.00g) was added and the mixture was stirred for 1 hour at room temperature. It was chilled in an ice bath. Ethyl 2-bromoacetate (2.77ml) was added and the solution was stirred for 18 hours until its temperature reached room temperature. Subsequently a saturated ammonium chloride aqua solution was added. After water was added to dilute the solution, extraction was performed using ether. After the organic layer was washed with water and a saturated saline solution, it was dried using anhydrous sodium sulfate. Subsequently, the solvent was removed under reduced pressure and the residuum was purified using silica gel column chromatography (developing solvent = ethyl acetate : n-hexane = 1:2). The target material (4.63g) was obtained in a yellow and oily form.

Example 10-16

In a similar manner as in Example 9, the compounds listed below (Table 2) were obtained, using ethyl 2-bromoacetate, or methyl 2-bromoacetate, or methyl 2-bromopropionate.

Table 2

(formula)

Example	R ¹	R ²	R ⁴	R ⁷	R ⁸	R	Yield (%)	Properties
10	Me	Et	H	Me	H	Me	78	Oily material with light yellow color
11	Et	Me	H	Et	H	Me	70	Oily material with light yellow color
12	Pr	Me	H	Et	H	Me	85	Oily material with yellow color
13	i - Pr	H	Me	Me	H	Me	77	Powder material with light yellow color
14	i - Pr	Me	H	Et	H	Me	69	Oily material with brown color
15	i - Pr	Et	H	Et	H	Me	69	Oily material with yellow color
16	cyclo-Pr	Me	H	Et	H	Me	37	Oily material with brown color

Example 17

4-(2-Methylpyrazolo[1, 5-a]pyridine-3-yl)-3-methyl-4-oxobutyric Acid

(Formula)

The compound of Example 9 (4.63g) was dissolved in 47% hydrobromic acid (50ml) and the solution was refluxed by heating for one hour. The solution was poured into an ice bath and extraction was performed using methylene chloride. After the

organic layer was dried using anhydrous sodium sulfate, the solvent was removed under reduced pressure. The residuum was purified using silica gel column chromatography (developing solvent = methylene chloride : ethanol = 10:1). The target material (2.76g) was obtained in a purple powder form.

Example 18-24

In a similar manner as in Example 17, the compounds listed below (Table 3) were obtained.

Table 3

(formula)

Example	R ¹	R ²	R ⁴	R ⁸	Yield (%)	Properties
18	Me	Et	H	H	78	Oily material with light yellow color
19	Et	Me	H	H	70	Oily material with light yellow color
20	Pr	Me	H	H	85	Oily material with yellow color
21	i - Pr	H	Me	H	77	Powder material with light yellow color
22	i - Pr	Me	H	H	69	Oily material with brown color
23	i - Pr	Et	H	H	69	Oily material with yellow color
24	cyclo-Pr	Me	H	H	37	Oily material with brown color

Example 25

4-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-3-phenyl-4-oxobutyric Acid Methyl Ester

(Formula)

2-Isopropyl-3-phenacylpyrazolo[1, 5-a]pyridine (1.90g) was dissolved in DMF (30ml). Sodium hydride (0.35g) was added and the mixture was stirred for 0.5 hours at room temperature. Then, 2-methyl bromoacetate (1.36g) was added and the solution was stirred for 3 hours at room temperature. Subsequently, a saturated ammonium chloride aqua solution was added. After water was added to dilute the solution, extraction was performed using ether. The organic layer was washed with water and a saturated saline solution. Then, it was dried using anhydrous sodium sulfate. Subsequently, the solvent was removed under reduced pressure and the residuum was purified using silica gel column chromatography (developing solvent = ethyl acetate : n-hexane = 1:3). The target material (1.58g) was obtained in a yellow and oily form.

Example 26

4-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-3-phenyl-4-oxobutyric Acid

(Formula)

The compound of Example 25 (1.58g) was dissolved in ethanol (15ml). Then, 1-N sodium hydroxide (5ml) was added and the mixture was stirred for 1 hour at room temperature. Water was added to the reaction solution. Subsequently, 10% hydrochloric acid was added to adjust its acidity to pH 3 and extraction was performed using methylene chloride. After the organic layer was dried using anhydrous sodium sulfate, the solvent was removed under reduced pressure. The target material (1.50g) was obtained in a colorless powder form.

Example 27

2,2-Diethoxycarbonyl-4-(2-isopropylpyrazolo[1, 5-a]pyridine-3-yl)-3-methyl-4-oxobutyric Acid Ethyl Ester

(Formula)

Triethoxycarbonylmethane (1.53g) was dissolved in DMF (20ml). Sodium hydride (0.28g) was added and the mixture was stirred for 0.5 hours at room temperature. 3-(2-Bromopropionyl)-2-isopropylpyrazolo[1, 5-a]pyridine (1.77g) was added and the solution was stirred for one hour at room temperature. Subsequently, it was stirred for 7 hours at 80 ~ 100 degrees Celsius. A saturated ammonium chloride aqua solution was added to the reaction solution. After water was added to dilute the solution, extraction was performed using ether. The organic layer was washed with water and a saturated saline solution. Then, it was dried using anhydrous sodium sulfate. Subsequently, the solvent was removed under reduced pressure and the residuum was purified using silica gel column chromatography (developing solvent = ethyl acetate : n-hexane = 1:2). The target material (0.67g) was obtained in a yellow and oily form.

Example 28

2-Ethoxycarbonyl-4-(2-isopropylpyrazolo[1, 5-a]pyridine-3-yl)-4-oxobutyric
Acid Ethyl Ester

(Formula)

Sodium (0.10g) was dissolved in ethanol (4ml). Then, diethyl malonate (0.71g) was added at room temperature. After the mixture was stirred for 20 minutes at 50 degrees Celsius, an ethanol solution (6ml) of 3-(2-bromoacetyl)-2-isopropylpyrazolo[1, 5-a]pyridine (1.06g) was added and the solution was stirred for 75 minutes at 80 degrees Celsius. The reaction solution was concentrated. Water and ethyl acetate were added to the residuum and the organic layer was separated. After the organic layer was washed with water and a saturated saline solution, it was dried using anhydrous sodium sulfate. Subsequently, the solvent was removed under reduced pressure and the residuum was purified using silica gel column chromatography (developing solvent = ethyl acetate : n-

hexane = 1:3). The target material (0.44g) was obtained in a powder form with a light yellow color.

Example 29

4-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-3-methyl-4-oxobutyric Acid

(Formula)

In a similar manner as in Example 17, the same compound (0.31g) as the target compound in Example 21 was obtained in an amorphous form with a light yellow color using the compound (0.67g) of Example 27.

Example 30

4-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-4-oxobutyric Acid

(Formula)

In a similar manner as in Example 17, the target compound (0.52g) was obtained in a colorless powder form using the compound (0.72g) of Example 28.

Example 31

6-(2-Methylpyrazolo[1, 5-a]pyridine-3-yl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

(Formula)

The compound of Example 17 (2.76g) and hydrazine monohydrate (0.90g) were dissolved in ethanol (30ml) and the solution was refluxed by heating for three hours. The solvent was removed from the reaction solution under reduced pressure. The residuum

was purified using silica gel column chromatography (developing solvent = methyl chloride : ethanol = 10:1). The target material (2.04g) was obtained in a colorless powder form. Recrystallization of this material in isopropyl ether produced colorless prism-shaped crystals. The melting point was 146 ~ 147 degrees Celsius.

Elemental analysis values (%): As $C_{13}H_{14}N_4O$

	C	H	N
Calculated values:	64.45	5.82	23.12
Measured values:	64.28	5.87	22.84

Example 32-40

In a similar manner as in Example 31, the compounds listed below (Table 4) were obtained.

Table 4

(formula)

Example	R ¹	R ²	R ⁴	R ⁶	R ⁸	Yield (%)	Melting Point (°C) (Recrystallization solvent)	Elemental Analysis Values Calculated values / Measured values C, H, N
32	Me	Et	H	H	H	80	138 ~ 140 <i>i</i> -Pr ₂ O	C ₁₄ H ₁₆ N ₄ O 65.61 6.29 21.86 65.70 6.31 21.72
33	Et	Me	H	H	H	79	131 ~ 132 <i>i</i> -Pr ₂ O	C ₁₄ H ₁₆ N ₄ O 65.61 6.29 21.86 65.74 6.22 21.85
34	Pr	Me	H	H	H	66	141 ~ 142 <i>i</i> -Pr ₂ O	C ₁₃ H ₁₄ N ₄ O 66.65 6.71 20.73 66.43 6.64 20.50
35	<i>i</i> -Pr	H	H	H	H	86	213.5 ~ 215.5 EtOH	C ₁₄ H ₁₆ N ₄ O 65.61 6.29 21.86 65.33 6.31 21.70
36	<i>i</i> -Pr	Me	H	H	H	50	119 ~ 122 <i>i</i> -Pr ₂ O	C ₁₅ H ₁₈ N ₄ O 66.65 6.71 20.73 66.54 6.73 20.67
37	<i>i</i> -Pr	Et	H	H	H	77	147 <i>i</i> -Pr ₂ O	C ₁₆ H ₂₀ N ₄ O 67.58 7.09 19.70 67.47 7.05 19.62
38	<i>i</i> -Pr	Ph	H	H	H	55	192 ~ 193 <i>i</i> -Pr ₂ O	C ₂₀ H ₂₀ N ₄ O 71.49 6.12 16.67 71.81 6.25 16.27 (1/5 H ₂ O adduct)
39	<i>i</i> -Pr	H	Me	H	H	86	207 ~ 208 EtOH	C ₁₅ H ₁₈ N ₄ O 66.65 6.71 20.73 66.65 6.58 20.74
40	cyclo-Pr	Me	H	H	H	79	134 <i>i</i> -Pr ₂ O	C ₁₅ H ₁₆ N ₄ O 67.15 6.01 20.88 67.31 6.07 20.85

Example 41

6-(2-Methylpyrazolo[1, 5-a]pyridine-3-yl)-5-methyl-3(2H)-pyridazinone

(Formula)

The compound of Example 36 (1.00g) was dissolved in acetic acid (30ml). As it was being stirred, bromine (0.22ml) was added. The solution was stirred for 0.5 hours. The reaction solution was poured into water. Extraction was performed using methylene chloride. After the organic layer was washed with water and a saturated sodium hydrogencarbonate aqua solution, it was dried using anhydrous sodium sulfate. Then, the solvent was removed from the reaction solution under reduced pressure. The residuum was purified using silica gel column chromatography (developing solvent = methyl chloride : ethanol = 15:1). The target material (0.69g) was obtained in a powder form with a light purple color. Recrystallization of this material in ethyl acetate produced prism-shaped crystals with a light purple color. The melting point was 216 ~ 217 degrees Celsius.

Elemental analysis values (%): As C₁₄H₁₄N₄O

	C	H	N
Calculated values:	66.13	5.55	22.03
Measured values:	65.96	5.49	21.90

Example 42-43

In a similar manner as in Example 41, the compounds listed below (Table 5) were obtained.

Table 5

(formula)

Example	R ¹	R ²	R ⁴	Yield (%)	Melting Point (°C) (Recrystallization solvent)	Elemental Analysis Values Calculated values / Measured values C, H, N
42	i-Pr	H	Me	71	216 ~ 217 AcOEt	C ₁₅ H ₁₆ N ₄ O 67.15 6.01 20.88 66.95 5.97 20.82
43	i-Pr	H	H	73	134 AcOEt	C ₁₄ H ₁₄ N ₄ O 65.66 5.59 21.88 65.43 5.56 21.64 (1/10 H ₂ O adduct)

(Table 5)

Example 44

(-)-6-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone and (+)-6-(2-Isopropylpyrazolo[1, 5-a]pyridine-3-yl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

The compound of Example 36 (1.36g) was dissolved in a 65ml mixture of ethanol and hexane (1 : 4). This solution was automatically fractionated using HPLC (optical division column manufactured by Chiralcell OD Daiseru Kagaku Kougyou: the transport layer = hexane : isopropanol = 9:1, the poured amount = 1ml, flow rate = 24 ml/minute, detection wavelength = 293nm). The compounds in each of the obtained fractions were recrystallized using diisopropyl ether. From the earlier fractions, 530mg of the (-) isomer was obtained as a colorless powder form, and from the latter fractions, 560mg of the (+) isomer was obtained as a colorless powder form.

The (-) isomer: Melting point = 164 ~ 165 degrees Celsius
Angle of rotation $[\alpha]_D^{34} = -179$ (C=0.24, CHCl₃)

Elemental analysis values (%): As C₁₅H₁₈N₄O

	C	H	N
Calculated values:	66.66	6.71	20.73
Measured values:	66.50	6.64	20.67

The (+) isomer: Melting point = 164 ~ 165 degrees Celsius
 Angle of rotation $[\alpha]_D^{34} = +179$ (C=0.24, CHCl₃)

Elemental analysis values (%): As C₁₅H₁₈N₄O

	C	H	N
Calculated values:	66.66	6.71	20.73
Measured values:	66.26	6.75	20.48

Experimental example

Measurement of phosphodiesterase inhibitory activity

Fractions containing phosphodiesterase were extracted from airways and hearts of *cavia porcellus*, using the method by Nicholson, et. al. (Br. J. Pharmacol., 97, 889-897 (1989)). These were used as an enzyme solution. The measurement of the phosphodiesterase inhibitory activity was performed by the determination (Linden, et. al, J, Immunol. Methods., 151, 209-216 (1992)) using the remaining amount of cyclic AMP (cAMP) or cyclic GMP (cGMP) after the enzyme reaction (Thompson, et. al., Biochemistry, 10, 311-316 (1971)).

1) Enzyme reaction

This was performed in accordance with the method by Thompson, et. al. The enzyme solution was placed in test tubes, and 1 μM cAMP or cGMP was added as a

substrate. After the reaction was carried out for 60 minutes at 30 degrees Celsius, the test tubes were placed in a boiling bath for 2 minutes in order to make the phosphodiesterase inactive and to stop the reaction. The compound under test was added to the test tubes at the same time as the substrate was added.

2) Determination by EIA

The remaining amount of cAMP or cGMP which was not decomposed by the enzyme solution was determined using the EIA kit (Amasham, England) for cAMP or cGMP determination. The amount of the material under test necessary to inhibit 50% of the enzyme reaction was defined as IC_{50} , and the results are shown in Table 6.

Table 6

	IC ₅₀ (μg/ml)						
	Airway				Heart		
	II	III	IV	V	I	II	III
Example 36	>30	4	5	0.1	>30	>30	5

Industrial application potential

The compounds of the present invention show an inhibitory effect which is selective against the airway-derived phosphodiesterase, in particular against phosphodiesterase V.

What is claimed is:

1 Pyrazolopyridylpyridazinone derivatives having a characteristic in that they are expressed by general formula (1),

Formula (1), (1)

and pharmacologically acceptable salts thereof, [wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^3 , R^4 , and R^5 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; and moreover, R^3 and R^5 may bond to each other to form a double bond.]

2 Bronchodilator having as its active ingredient at least one of the pyrazolopyridylpyridazinone derivatives a characteristic in that they are expressed by general formula (1),

Formula (1), (1)

and pharmacologically acceptable salts thereof, [wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^3 , R^4 , and R^5 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; and moreover, R^3 and R^5 may bond to each other to form a double bond.]

3 Production method of the compounds expressed by general formula (5),

Formula (5) (5)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^4 , R^6 , and R^8 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; and R^7 is a lower alkyl group having 1 ~ 3 carbon atoms,]

wherein the production method is characterized by reacting the compounds expressed by general formula (2)

Formula (2) (2)

[wherein R^1 , R^2 , and R^6 are the same as previously described,] with the compounds expressed by general formula (4)

Formula (4) (4)

[and wherein X is a halogen atom; and R^4 , R^7 , and R^8 are the same as previously described.]

4 Production method of the compounds expressed by general formula (5a),

Formula (5a) (5a)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^4 , and R^8 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; R^7 is a lower alkyl group having 1 ~ 3 carbon atoms; R^9 is a lower alkoxy carbonyl group having 1 ~ 3 carbon atoms,]

wherein the production method is characterized by reacting the compounds expressed by general formula (2a)

Formula (2a) (2a)

[wherein R^1 and R^2 are the same as previously described,] with the compounds expressed by general formula (3),

$CO(OR)_2$ (3)

[wherein R is the same as previously described,] and then with the compounds expressed by general formula (4)

Formula (4) (4)

[wherein X is a halogen atom; and R^4 , R^7 , and R^8 are the same as previously described.]

5 Production method of the compounds expressed by general formula (6),

Formula (6) (6)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , R^4 , and R^8 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; and R^6 is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group,]

and wherein the production method is characterized by hydrolyzing and if necessary decarboxylating the compounds expressed by general formula (5a).

Formula (5b) (5b)

[wherein R^1 , R^2 , R^4 , and R^8 are the same as previously described; R^7 is a lower alkyl group having 1 ~ 3 carbon atoms; and R^{10} is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, a phenyl group, or a lower alkoxy carbonyl group having 1 ~ 3 carbon atoms.]

6 Production method of the compounds expressed by general formula (9),

Formula (9) (9)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; R^2 , and R^6 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group; R^{11} is a lower alkyl group having 1 ~ 3 carbon atoms; and (n, m) is a combination of integers, (1, 3) or (2, 2),]

wherein the production method is characterized by reacting the compounds expressed by general formula (7),

Formula (7) (7)

[wherein R^1 , R^2 and R^6 are the same as previously described; and X is a halogen atom,]
with the compounds expressed by general formula (8),

$CH_n(CO_2R^{11})_m$ (8)

[wherein the combination of (n, m) and R^{11} are the same as previously described.]

7 Production method of the compounds expressed by general formula (6b),

Formula (6b)

(6b)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; and R^2 , and R^6 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group,]

and wherein the production method is characterized by hydrolyzing and decarboxylating the compounds expressed by general formula (9),

Formula (9)

(9)

[wherein R^1 , R^2 and R^6 are the same as previously described; R^{11} is a lower alkyl group having 1 ~ 3 carbon atoms; X is a halogen atom; and (n, m) is a combination of integers, (1, 3) or (2, 2).]

8 Production method of the compounds expressed by general formula (1a),

Formula (1a)

(1a)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; and R^2 , R^4 , R^6 , and R^8 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group,]

and wherein the production method is characterized by reacting the compounds expressed by general formula (6) with hydrazine,

Formula (6)

(6)

[wherein R^1 , R^2 , R^4 , R^6 , and R^8 are the same as previously described.]

9 Production method of the compounds expressed by general formula (1c),

Formula (1c) (1c)

[wherein R^1 is a lower alkyl group having 1 ~ 4 carbon atoms, or a cycloalkyl group having 3 ~ 6 carbon atoms; and R^2 and R^4 could be the same or different, and each of them is a hydrogen atom, a lower alkyl group having 1 ~ 4 carbon atoms, or a phenyl group,]

and wherein the production method is characterized by oxidizing the compounds expressed by general formula (1b),

Formula (1b) (1b)

[wherein R^1 , R^2 and R^4 are the same as previously described.]